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- (71) Applicant: ALEXZA MOLECULAR DELIVERY CORPORATION [US/US]; 1001 E. Meadow Circle, Palo Alto, CA 94303 (US).
- (72) Inventors: RABINOWITZ, Joshua, D.; 750 N. Shoreline Blvd., #50, Mountain View, CA 94043 (US). ZAFARONI, Alejandro, C.; 1 Faxon Forest, Atherton, CA 94027 (US).
- (74) Agents: ECKMAN, Richard, R. et al.; Morrison & Foerster LLP, 755 Page Mill Road, Palo Alto, CA 94304-1018 (US).
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(54) Title: DELIVERY OF ANTIPSYCHOTICS THROUGH AN INHALATION ROUTE

(57) Abstract: The present invention relates to the delivery of antipsychotics through an inhalation route. Specifically, it relates to aerosols containing antipsychotics that are used in inhalation therapy. In a composition aspect of the present invention, the aerosol comprises particles comprising at least 5 percent by weight of an antipsychotic. In a method aspect of the present invention, an antipsychotic is delivered to a mammal through an inhalation route. The method comprises: a) Heating a composition, wherein the composition comprises at least 5 percent by weight of an antipsychotic, to form a vapor; and, b) allowing the vapor to cool, thereby forming a condensation aerosol comprising particles, which is inhaled by the mammal. In a kit aspect of the present invention, a kit for delivering an antipsychotic through an inhalation route to a mammal is provided which comprises: a) a composition comprising at least 5 percent by weight of an antipsychotic; and, b) a device that forms an antipsychotic containing aerosol from the composition, for inhalation by the mammal.

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## **DELIVERY OF ANTIPSYCHOTICS THROUGH AN INHALATION ROUTE**

**[0001]** This application claims priority to U.S. provisional application Ser. No. 60/294,203 entitled "Thermal Vapor Delivery of Drugs," filed May 24, 2001, Rabinowitz and Zaffaroni, the entire disclosure of which is hereby incorporated by reference. This application further claims priority to U.S. provisional application Ser. No. 60/317,479 entitled "Aerosol Drug Delivery," filed September 5, 2001, Rabinowitz and Zaffaroni, the entire disclosure of which is hereby incorporated by reference.

### **Field of the Invention**

**[0002]** The present invention relates to the delivery of antipsychotics through an inhalation route. Specifically, it relates to aerosols containing antipsychotics that are used in inhalation therapy.

### **Background of the Invention**

**[0003]** There are a number of compositions currently marketed for the treatment of psychosis. The compositions contain at least one active ingredient that provides for observed therapeutic effects. Among the active ingredients given in antipsychotic compositions are olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine, and fluphenazine.

**[0004]** It is desirable to provide a new route of administration for antipsychotics that rapidly produces peak plasma concentrations of active compound. The provision of such a route is an object of the present invention.

### **Summary of the Invention**

**[0005]** The present invention relates to the delivery of antipsychotics through an inhalation route. Specifically, it relates to aerosols containing antipsychotics that are used in inhalation therapy.

**[0006]** In a composition aspect of the present invention, the aerosol comprises particles comprising at least 5 percent by weight of an antipsychotic. Preferably, the particles

comprise at least 10 percent by weight of an antipsychotic. More preferably, the particles comprise at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 97 percent, 99 percent, 99.5 percent or 99.97 percent by weight of an antipsychotic.

[0007] Typically, the aerosol has a mass of at least 10 µg. Preferably, the aerosol has a mass of at least 100 µg. More preferably, the aerosol has a mass of at least 200 µg.

[0008] Typically, the particles comprise less than 10 percent by weight of antipsychotic degradation products. Preferably, the particles comprise less than 5 percent by weight of antipsychotic degradation products. More preferably, the particles comprise less than 2.5, 1, 0.5, 0.1 or 0.03 percent by weight of antipsychotic degradation products.

[0009] Typically, the particles comprise less than 90 percent by weight of water. Preferably, the particles comprise less than 80 percent by weight of water. More preferably, the particles comprise less than 70 percent, 60 percent, 50 percent, 40 percent, 30 percent, 20 percent, 10 percent, or 5 percent by weight of water.

[0010] Typically, at least 50 percent by weight of the aerosol is amorphous in form, wherein crystalline forms make up less than 50 percent by weight of the total aerosol weight, regardless of the nature of individual particles. Preferably, at least 75 percent by weight of the aerosol is amorphous in form. More preferably, at least 90 percent by weight of the aerosol is amorphous in form.

[0011] Typically, the aerosol particles have a mass median aerodynamic diameter of less than 5 microns. Preferably, the particles have a mass median aerodynamic diameter of less than 3 microns. More preferably, the particles have a mass median aerodynamic diameter of less than 2 or 1 micron(s).

[0012] Typically, the geometric standard deviation around the mass median aerodynamic diameter of the aerosol particles is less than 3.0. Preferably, the geometric standard deviation is less than 2.5. More preferably, the geometric standard deviation is less than 2.1.

[0013] Typically, the aerosol is formed by heating a composition containing an antipsychotic to form a vapor and subsequently allowing the vapor to condense into an aerosol.

[0014] Typically, the antipsychotic is a typical antipsychotic or an atypical antipsychotic.

[0015] In another composition aspect of the present invention, the aerosol comprises particles comprising at least 5 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine, or fluphenazine. Preferably, the particles comprise at least 10 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine, or fluphenazine. More preferably, the particles comprise at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 97 percent, 99 percent, 99.5 percent or 99.97 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine, or fluphenazine.

[0016] Typically, the aerosol has a mass of at least 10 µg. Preferably, the aerosol has a mass of at least 100 µg. More preferably, the aerosol has a mass of at least 200 µg.

[0017] Typically, the particles comprise less than 10 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine, or fluphenazine degradation products. Preferably, the particles comprise less than 5 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine, or fluphenazine degradation products. More preferably, the particles comprise less than 2.5, 1, 0.5, 0.1 or 0.03 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine, or fluphenazine degradation products.

[0018] Typically, the particles comprise less than 90 percent by weight of water. Preferably, the particles comprise less than 80 percent by weight of water. More preferably, the particles comprise less than 70 percent, 60 percent, 50 percent, 40 percent, 30 percent, 20 percent, 10 percent, or 5 percent by weight of water.

[0019] Typically, at least 50 percent by weight of the aerosol is amorphous in form, wherein crystalline forms make up less than 50 percent by weight of the total aerosol

weight, regardless of the nature of individual particles. Preferably, at least 75 percent by weight of the aerosol is amorphous in form. More preferably, at least 90 percent by weight of the aerosol is amorphous in form.

[0020] Typically, where the aerosol comprises olanzapine, the aerosol has an inhalable aerosol drug mass density of between 0.2 mg/L and 20 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 0.5 mg/L and 10 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 1 mg/L and 5 mg/L.

[0021] Typically, where the aerosol comprises trifluoperazine, the aerosol has an inhalable aerosol drug mass density of between 0.2 mg/L and 10 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 0.5 mg/L and 8 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 1 mg/L and 5 mg/L.

[0022] Typically, where the aerosol comprises haloperidol, the aerosol has an inhalable aerosol drug mass density of between 0.2 mg/L and 10 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 0.5 mg/L and 8 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 1 mg/L and 5 mg/L.

[0023] Typically, where the aerosol comprises loxapine, the aerosol has an inhalable aerosol drug mass density of between 2 mg/L and 100 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 5 mg/L and 80 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 10 mg/L and 50 mg/L.

[0024] Typically, where the aerosol comprises risperidone, the aerosol has an inhalable aerosol drug mass density of between 0.1 mg/L and 5 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 0.2 mg/L and 3 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 0.4 mg/L and 2 mg/L.

[0025] Typically, where the aerosol comprises clozapine, the aerosol has an inhalable aerosol drug mass density of between 2 mg/L and 200 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 4 mg/L and 150 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 10 mg/L and 100 mg/L.

[0026] Typically, where the aerosol comprises quetiapine, the aerosol has an inhalable aerosol drug mass density of between 2 mg/L and 200 mg/L. Preferably, the aerosol has an

inhalable aerosol drug mass density of between 4 mg/L and 150 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 10 mg/L and 100 mg/L.

[0027] Typically, where the aerosol comprises promazine, the aerosol has an inhalable aerosol drug mass density of between 2 mg/L and 200 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 4 mg/L and 150 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 10 mg/L and 100 mg/L.

[0028] Typically, where the aerosol comprises thiothixene, the aerosol has an inhalable aerosol drug mass density of between 0.5 mg/L and 20 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 1 mg/L and 10 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 2 mg/L and 8 mg/L.

[0029] Typically, where the aerosol comprises chlorpromazine, the aerosol has an inhalable aerosol drug mass density of between 2 mg/L and 200 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 4 mg/L and 150 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 5 mg/L and 100 mg/L.

[0030] Typically, where the aerosol comprises droperidol, the aerosol has an inhalable aerosol drug mass density of between 0.2 mg/L and 20 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 0.5 mg/L and 10 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 1 mg/L and 5 mg/L.

[0031] Typically, where the aerosol comprises prochlorperazine, the aerosol has an inhalable aerosol drug mass density of between 0.5 mg/L and 20 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 1 mg/L and 15 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 2 mg/L and 10 mg/L.

[0032] Typically, where the aerosol comprises fluphenazine, the aerosol has an inhalable aerosol drug mass density of between 0.1 mg/L and 10 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 0.2 mg/L and 8 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 0.5 mg/L and 5 mg/L.

[0033] Typically, the aerosol has an inhalable aerosol particle density greater than  $10^6$  particles/mL. Preferably, the aerosol has an inhalable aerosol particle density greater than  $10^7$  particles/mL or  $10^8$  particles/mL.

[0034] Typically, the aerosol particles have a mass median aerodynamic diameter of less than 5 microns. Preferably, the particles have a mass median aerodynamic diameter of less than 3 microns. More preferably, the particles have a mass median aerodynamic diameter of less than 2 or 1 micron(s).

[0035] Typically, the geometric standard deviation around the mass median aerodynamic diameter of the aerosol particles is less than 3.0. Preferably, the geometric standard deviation is less than 2.5. More preferably, the geometric standard deviation is less than 2.1.

[0036] Typically, the aerosol is formed by heating a composition containing olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine, or fluphenazine to form a vapor and subsequently allowing the vapor to condense into an aerosol.

[0037] In a method aspect of the present invention, an antipsychotic is delivered to a mammal through an inhalation route. The method comprises: a) heating a composition, wherein the composition comprises at least 5 percent by weight of an antipsychotic, to form a vapor; and, b) allowing the vapor to cool, thereby forming a condensation aerosol comprising particles, which is inhaled by the mammal. Preferably, the composition that is heated comprises at least 10 percent by weight of an antipsychotic. More preferably, the composition comprises at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 97 percent, 99 percent, 99.5 percent, 99.9 percent or 99.97 percent by weight of an antipsychotic.

[0038] Typically, the particles comprise at least 5 percent by weight of an antipsychotic. Preferably, the particles comprise at least 10 percent by weight of an antipsychotic. More preferably, the particles comprise at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 97 percent, 99 percent, 99.5 percent, 99.9 percent or 99.97 percent by weight of an antipsychotic.

[0039] Typically, the condensation aerosol has a mass of at least 10  $\mu\text{g}$ . Preferably, the aerosol has a mass of at least 100  $\mu\text{g}$ . More preferably, the aerosol has a mass of at least 200  $\mu\text{g}$ .

[0040] Typically, the particles comprise less than 10 percent by weight of antipsychotic degradation products. Preferably, the particles comprise less than 5 percent by weight of antipsychotic degradation products. More preferably, the particles comprise 2.5, 1, 0.5, 0.1 or 0.03 percent by weight of antipsychotic degradation products.

[0041] Typically, the particles comprise less than 90 percent by weight of water. Preferably, the particles comprise less than 80 percent by weight of water. More preferably, the particles comprise less than 70 percent, 60 percent, 50 percent, 40 percent, 30 percent, 20 percent, 10 percent, or 5 percent by weight of water.

[0042] Typically, at least 50 percent by weight of the aerosol is amorphous in form, wherein crystalline forms make up less than 50 percent by weight of the total aerosol weight, regardless of the nature of individual particles. Preferably, at least 75 percent by weight of the aerosol is amorphous in form. More preferably, at least 90 percent by weight of the aerosol is amorphous in form.

[0043] Typically, the particles of the delivered condensation aerosol have a mass median aerodynamic diameter of less than 5 microns. Preferably, the particles have a mass median aerodynamic diameter of less than 3 microns. More preferably, the particles have a mass median aerodynamic diameter of less than 2 or 1 micron(s).

[0044] Typically, the geometric standard deviation around the mass median aerodynamic diameter of the aerosol particles is less than 3.0. Preferably, the geometric standard deviation is less than 2.5. More preferably, the geometric standard deviation is less than 2.1.

[0045] Typically, the rate of inhalable aerosol particle formation of the delivered condensation aerosol is greater than  $10^8$  particles per second. Preferably, the aerosol is formed at a rate greater than  $10^9$  inhalable particles per second. More preferably, the aerosol is formed at a rate greater than  $10^{10}$  inhalable particles per second.

[0046] Typically, the delivered condensation aerosol is formed at a rate greater than 0.5 mg/second. Preferably, the aerosol is formed at a rate greater than 0.75 mg/second. More

preferably, the aerosol is formed at a rate greater than 1 mg/second, 1.5 mg/second or 2 mg/second.

[0047] Typically, the delivered condensation aerosol results in a peak plasma concentration of an antipsychotic in the mammal in less than 1 h. Preferably, the peak plasma concentration is reached in less than 0.5 h. More preferably, the peak plasma concentration is reached in less than 0.2, 0.1, 0.05, 0.02, 0.01, or 0.005 h (arterial measurement).

[0048] Typically, the antipsychotic is a typical antipsychotic or an atypical antipsychotic.

[0049] In another method aspect of the present invention, one of olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine, or fluphenazine is delivered to a mammal through an inhalation route. The method comprises: a) heating a composition, wherein the composition comprises at least 5 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine, or fluphenazine, to form a vapor; and, b) allowing the vapor to cool, thereby forming a condensation aerosol comprising particles, which is inhaled by the mammal. Preferably, the composition that is heated comprises at least 10 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine, or fluphenazine. More preferably, the composition comprises at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 97 percent, 99 percent, 99.5 percent, 99.9 percent or 99.97 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine, or fluphenazine.

[0050] Typically, the particles comprise at least 5 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine, or fluphenazine. Preferably, the particles comprise at least 10 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine,

droperidol, prochlorperazine, or fluphenazine. More preferably, the particles comprise at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 97 percent, 99 percent, 99.5 percent, 99.9 percent or 99.97 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine, or fluphenazine.

[0051] Typically, the condensation aerosol has a mass of at least 10  $\mu\text{g}$ . Preferably, the aerosol has a mass of at least 100  $\mu\text{g}$ . More preferably, the aerosol has a mass of at least 200  $\mu\text{g}$ .

[0052] Typically, the particles comprise less than 10 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine, or fluphenazine degradation products. Preferably, the particles comprise less than 5 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine, or fluphenazine degradation products. More preferably, the particles comprise 2.5, 1, 0.5, 0.1 or 0.03 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine, or fluphenazine degradation products.

[0053] Typically, the particles comprise less than 90 percent by weight of water. Preferably, the particles comprise less than 80 percent by weight of water. More preferably, the particles comprise less than 70 percent, 60 percent, 50 percent, 40 percent, 30 percent, 20 percent, 10 percent, or 5 percent by weight of water.

[0054] Typically, at least 50 percent by weight of the aerosol is amorphous in form, wherein crystalline forms make up less than 50 percent by weight of the total aerosol weight, regardless of the nature of individual particles. Preferably, at least 75 percent by weight of the aerosol is amorphous in form. More preferably, at least 90 percent by weight of the aerosol is amorphous in form.

[0055] Typically, the particles of the delivered condensation aerosol have a mass median aerodynamic diameter of less than 5 microns. Preferably, the particles have a mass

median aerodynamic diameter of less than 3 microns. More preferably, the particles have a mass median aerodynamic diameter of less than 2 or 1 micron(s).

[0056] Typically, the geometric standard deviation around the mass median aerodynamic diameter of the aerosol particles is less than 3.0. Preferably, the geometric standard deviation is less than 2.5. More preferably, the geometric standard deviation is less than 2.1.

[0057] Typically, where the aerosol comprises olanzapine, the delivered aerosol has an inhalable aerosol drug mass density of between 0.2 mg/L and 20 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 0.5 mg/L and 10 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 1 mg/L and 5 mg/L.

[0058] Typically, where the aerosol comprises trifluoperazine, the delivered aerosol has an inhalable aerosol drug mass density of between 0.2 mg/L and 10 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 0.5 mg/L and 8 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 1 mg/L and 5 mg/L.

[0059] Typically, where the aerosol comprises haloperidol, the delivered aerosol has an inhalable aerosol drug mass density of between 0.2 mg/L and 10 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 0.5 mg/L and 8 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 1 mg/L and 5 mg/L.

[0060] Typically, where the aerosol comprises loxapine, the delivered aerosol has an inhalable aerosol drug mass density of between 2 mg/L and 100 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 5 mg/L and 80 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 10 mg/L and 50 mg/L.

[0061] Typically, where the aerosol comprises risperidone, the delivered aerosol has an inhalable aerosol drug mass density of between 0.1 mg/L and 5 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 0.2 mg/L and 3 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 0.4 mg/L and 2 mg/L.

[0062] Typically, where the aerosol comprises clozapine, the delivered aerosol has an inhalable aerosol drug mass density of between 2 mg/L and 200 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 4 mg/L and 150 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 10 mg/L and 100 mg/L.

[0063] Typically, where the aerosol comprises quetiapine, the delivered aerosol has an inhalable aerosol drug mass density of between 2 mg/L and 200 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 4 mg/L and 150 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 10 mg/L and 100 mg/L.

[0064] Typically, where the aerosol comprises promazine, the delivered aerosol has an inhalable aerosol drug mass density of between 2 mg/L and 200 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 4 mg/L and 150 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 10 mg/L and 100 mg/L.

[0065] Typically, where the aerosol comprises thiothixene, the delivered aerosol has an inhalable aerosol drug mass density of between 0.5 mg/L and 20 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 1 mg/L and 10 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 2 mg/L and 8 mg/L.

[0066] Typically, where the aerosol comprises chlorpromazine, the delivered aerosol has an inhalable aerosol drug mass density of between 2 mg/L and 200 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 4 mg/L and 150 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 5 mg/L and 100 mg/L.

[0067] Typically, where the aerosol comprises droperidol, the delivered aerosol has an inhalable aerosol drug mass density of between 0.2 mg/L and 20 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 0.5 mg/L and 10 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 1 mg/L and 5 mg/L.

[0068] Typically, where the aerosol comprises prochlorperazine, the delivered aerosol has an inhalable aerosol drug mass density of between 0.5 mg/L and 20 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 1 mg/L and 15 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 2 mg/L and 10 mg/L.

[0069] Typically, where the aerosol comprises fluphenazine, the delivered aerosol has an inhalable aerosol drug mass density of between 0.1 mg/L and 10 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 0.2 mg/L and 8 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 0.5 mg/L and 5 mg/L.

[0070] Typically, the delivered aerosol has an inhalable aerosol particle density greater than  $10^6$  particles/mL. Preferably, the aerosol has an inhalable aerosol particle density greater than  $10^7$  particles/mL or  $10^8$  particles/mL.

[0071] Typically, the rate of inhalable aerosol particle formation of the delivered condensation aerosol is greater than  $10^8$  particles per second. Preferably, the aerosol is formed at a rate greater than  $10^9$  inhalable particles per second. More preferably, the aerosol is formed at a rate greater than  $10^{10}$  inhalable particles per second.

[0072] Typically, the delivered condensation aerosol is formed at a rate greater than 0.5 mg/second. Preferably, the aerosol is formed at a rate greater than 0.75 mg/second. More preferably, the aerosol is formed at a rate greater than 1 mg/second, 1.5 mg/second or 2 mg/second.

[0073] Typically, where the condensation aerosol comprises olanzapine, between 0.2 mg and 20 mg of olanzapine are delivered to the mammal in a single inspiration. Preferably, between 0.5 mg and 10 mg of olanzapine are delivered to the mammal in a single inspiration. More preferably, between 1 mg and 5 mg of olanzapine are delivered to the mammal in a single inspiration.

[0074] Typically, where the condensation aerosol comprises trifluoperazine, between 0.2 mg and 10 mg of trifluoperazine are delivered to the mammal in a single inspiration. Preferably, between 0.5 mg and 8 mg of trifluoperazine are delivered to the mammal in a single inspiration. More preferably, between 1 mg and 5 mg of trifluoperazine are delivered to the mammal in a single inspiration.

[0075] Typically, where the condensation aerosol comprises haloperidol, between 0.2 mg and 10 mg of haloperidol are delivered to the mammal in a single inspiration. Preferably, between 0.5 mg and 8 mg of haloperidol are delivered to the mammal in a single inspiration. More preferably, between 1 mg and 5 mg of haloperidol are delivered to the mammal in a single inspiration.

[0076] Typically, where the condensation aerosol comprises loxapine, between 2 mg and 100 mg of loxapine are delivered to the mammal in a single inspiration. Preferably, between 5 mg and 80 mg of loxapine are delivered to the mammal in a single inspiration. More preferably, between 10 mg and 50 mg of loxapine are delivered to the mammal in a single inspiration.

[0077] Typically, where the condensation aerosol comprises risperidone, between 0.1 mg and 5 mg of risperidone are delivered to the mammal in a single inspiration. Preferably, between 0.2 mg and 3 mg of risperidone are delivered to the mammal in a single inspiration. More preferably, between 0.4 mg and 2 mg of risperidone are delivered to the mammal in a single inspiration.

[0078] Typically, where the condensation aerosol comprises clozapine, between 2 mg and 200 mg of clozapine are delivered to the mammal in a single inspiration. Preferably, between 4 mg and 150 mg of clozapine are delivered to the mammal in a single inspiration. More preferably, between 10 mg and 100 mg of clozapine are delivered to the mammal in a single inspiration.

[0079] Typically, where the condensation aerosol comprises quetiapine, between 2 mg and 200 mg of quetiapine are delivered to the mammal in a single inspiration. Preferably, between 4 mg and 150 mg of quetiapine are delivered to the mammal in a single inspiration. More preferably, between 10 mg and 100 mg of quetiapine are delivered to the mammal in a single inspiration.

[0080] Typically, where the condensation aerosol comprises promazine, between 2 mg and 200 mg of promazine are delivered to the mammal in a single inspiration. Preferably, between 4 mg and 150 mg of promazine are delivered to the mammal in a single inspiration. More preferably, between 10 mg and 100 mg of promazine are delivered to the mammal in a single inspiration.

[0081] Typically, where the condensation aerosol comprises thiothixene, between 0.5 mg and 20 mg of thiothixene are delivered to the mammal in a single inspiration. Preferably, between 1 mg and 10 mg of thiothixene are delivered to the mammal in a single inspiration. More preferably, between 2 mg and 8 mg of thiothixene are delivered to the mammal in a single inspiration.

[0082] Typically, where the condensation aerosol comprises chlorpromazine, between 2 mg and 200 mg of chlorpromazine are delivered to the mammal in a single inspiration. Preferably, between 4 mg and 150 mg of chlorpromazine are delivered to the mammal in a single inspiration. More preferably, between 5 mg and 100 mg of chlorpromazine are delivered to the mammal in a single inspiration.

[0083] Typically, where the condensation aerosol comprises droperidol, between 0.2 mg and 20 mg of droperidol are delivered to the mammal in a single inspiration. Preferably, between 0.5 mg and 10 mg of droperidol are delivered to the mammal in a single inspiration. More preferably, between 1 mg and 5 mg of droperidol are delivered to the mammal in a single inspiration.

[0084] Typically, where the condensation aerosol comprises prochlorperazine, between 0.5 mg and 20 mg of prochlorperazine are delivered to the mammal in a single inspiration. Preferably, between 1 mg and 15 mg of prochlorperazine are delivered to the mammal in a single inspiration. More preferably, between 2 mg and 10 mg of prochlorperazine are delivered to the mammal in a single inspiration.

[0085] Typically, where the condensation aerosol comprises fluphenazine, between 0.1 mg and 10 mg of fluphenazine are delivered to the mammal in a single inspiration. Preferably, between 0.2 mg and 8 mg of fluphenazine are delivered to the mammal in a single inspiration. More preferably, between 0.5 mg and 5 mg of fluphenazine are delivered to the mammal in a single inspiration.

[0086] Typically, the delivered condensation aerosol results in a peak plasma concentration of olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine, or fluphenazine in the mammal in less than 1 h. Preferably, the peak plasma concentration is reached in less than 0.5 h. More preferably, the peak plasma concentration is reached in less than 0.2, 0.1, 0.05, 0.02, 0.01, or 0.005 h (arterial measurement).

[0087] Typically, the delivered condensation aerosol is used to treat psychosis.

[0088] In a kit aspect of the present invention, a kit for delivering an antipsychotic through an inhalation route to a mammal is provided which comprises: a) a composition comprising at least 5 percent by weight of an antipsychotic; and, b) a device that forms an antipsychotic aerosol from the composition, for inhalation by the mammal. Preferably, the composition comprises at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 97 percent, 99 percent, 99.5 percent, 99.9 percent or 99.97 percent by weight of an antipsychotic.

[0089] Typically, the device contained in the kit comprises: a) an element for heating the antipsychotic composition to form a vapor; b) an element allowing the vapor to cool to form an aerosol; and, c) an element permitting the mammal to inhale the aerosol.

[0090] In a kit aspect of the present invention, a kit for delivering olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine, or fluphenazine through an inhalation route to a mammal is provided which comprises: a) a composition comprising at least 5 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine, or fluphenazine; and, b) a device that forms a olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine, or fluphenazine aerosol from the composition, for inhalation by the mammal. Preferably, the composition comprises at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 97 percent, 99 percent, 99.5 percent, 99.9 percent or 99.97 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine, or fluphenazine.

[0091] Typically, the device contained in the kit comprises: a) an element for heating the olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine, or fluphenazine composition to form a vapor; b) an element allowing the vapor to cool to form an aerosol; and, c) an element permitting the mammal to inhale the aerosol.

### Brief Description of the Figure

[0092] Fig. 1 shows a cross-sectional view of a device used to deliver antipsychotic aerosols to a mammal through an inhalation route.

### Detailed Description of the Invention

#### *Definitions*

[0093] “Aerodynamic diameter” of a given particle refers to the diameter of a spherical droplet with a density of 1 g/mL (the density of water) that has the same settling velocity as the given particle.

[0094] “Aerosol” refers to a suspension of solid or liquid particles in a gas.

[0095] “Aerosol drug mass density” refers to the mass of an antipsychotic per unit volume of aerosol.

[0096] “Aerosol mass density” refers to the mass of particulate matter per unit volume of aerosol.

[0097] “Aerosol particle density” refers to the number of particles per unit volume of aerosol.

[0098] “Amorphous particle” refers to a particle that does not contain more than 50 percent by weight of a crystalline form. Preferably, the particle does not contain more than 25 percent by weight of a crystalline form. More preferably, the particle does not contain more than 10 percent by weight of a crystalline form.

[0099] “Antipsychotic degradation product” refers to a compound resulting from a chemical modification of an antipsychotic. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis.

[0100] “Chlorpromazine” refers to 10-(3-dimethylaminopropyl)-2-chlorophenothiazine.

[0101] “Chlorpromazine degradation product” refers to a compound resulting from a chemical modification of chlorpromazine. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis.

[0102] “Clozapine” refers to 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e]-[1,4]benzodiazepine.

[0103] "Clozapine degradation product" refers to a compound resulting from a chemical modification of clozapine. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis. Examples of degradation products include compounds of molecular formula C<sub>6</sub>H<sub>12</sub>N<sub>2</sub>O and C<sub>13</sub>H<sub>8</sub>N<sub>2</sub>Cl.

[0104] "Droperidol" refers to 1-[1-[4-(4-fluorophenyl)-4-oxobutyl]-1,2,3,6-tetrahydro-4-pyridinyl]-1,3-dihydro-2H-benzimidazol-2-one.

[0105] "Droperidol degradation product" refers to a compound resulting from a chemical modification of droperidol. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis. An example of a degradation product is 2-hydroxybenzimidazole.

[0106] "Condensation aerosol" refers to an aerosol formed by vaporization of a substance followed by condensation of the substance into an aerosol.

[0107] "Fluphenazine" refers to 4-[3-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]propyl]-1-piperazine-ethanol.

[0108] "Fluphenazine degradation product" refers to a compound resulting from a chemical modification of fluphenazine. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis. Examples of degradation products include C<sub>13</sub>H<sub>8</sub>NSF<sub>3</sub> (removal of substituted propyl chain from nitrogen) and C<sub>13</sub>H<sub>8</sub>NOSF<sub>3</sub> (oxidation of C<sub>13</sub>H<sub>8</sub>NSF<sub>3</sub>).

[0109] "Haloperidol" refers to 4-[4-(p-chlorophenyl)-4-hydroxypiperidinol]-4'-fluorobutyrophenone.

[0110] "Haloperidol degradation product" refers to a compound resulting from a chemical modification of haloperidol. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis. An example of a degradation product is a compound of molecular formula C<sub>11</sub>H<sub>14</sub>NOCl (removal of substituted propyl sidechain from nitrogen).

[0111] "Inhalable aerosol drug mass density" refers to the aerosol drug mass density produced by an inhalation device and delivered into a typical patient tidal volume.

[0112] "Inhalable aerosol mass density" refers to the aerosol mass density produced by an inhalation device and delivered into a typical patient tidal volume.

[0113] "Inhalable aerosol particle density" refers to the aerosol particle density of particles of size between 100 nm and 5 microns produced by an inhalation device and delivered into a typical patient tidal volume.

[0114] "Loxapine" refers to 2-chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f]-[1,4]diazepine.

[0115] "Loxapine degradation product" refers to a compound resulting from a chemical modification of loxapine. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis.

[0116] "Mass median aerodynamic diameter" or "MMAD" of an aerosol refers to the aerodynamic diameter for which half the particulate mass of the aerosol is contributed by particles with an aerodynamic diameter larger than the MMAD and half by particles with an aerodynamic diameter smaller than the MMAD.

[0117] "Olanzapine" refers to 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine.

[0118] "Olanzapine degradation product" refers to a compound resulting from a chemical modification of olanzapine. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis. Examples of degradation products are C<sub>12</sub>H<sub>10</sub>N<sub>2</sub>OS (replacement of piperazine group with OH) and C<sub>5</sub>H<sub>12</sub>N<sub>2</sub> (1-methylpiperazine).

[0119] "Prochlorperazine" refers to 2-chloro-10-[3-(4-methyl-1-piperazinyl)propyl]-10H-phenothiazine.

[0120] "Prochlorperazine degradation product" refers to a compound resulting from a chemical modification of prochlorperazine. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis.

[0121] "Promazine" refers to N,N-dimethyl-10H-phenothiazine-10-propanamine.

[0122] "Promazine degradation product" refers to a compound resulting from a chemical modification of promazine. The modification, for example, can be the result of a

thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis.

[0123] "Quetiapine" refers to 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)-ethoxy]-ethanol.

[0124] "Quetiapine degradation product" refers to a compound resulting from a chemical modification of quetiapine. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis.

[0125] "Rate of aerosol formation" refers to the mass of aerosolized particulate matter produced by an inhalation device per unit time.

[0126] "Rate of inhalable aerosol particle formation" refers to the number of particles of size between 100 nm and 5 microns produced by an inhalation device per unit time.

[0127] "Rate of drug aerosol formation" refers to the mass of aerosolized antipsychotic produced by an inhalation device per unit time.

[0128] "Risperidone" refers to 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one.

[0129] "Risperidone degradation product" refers to a compound resulting from a chemical modification of risperidone. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis.

[0130] "Settling velocity" refers to the terminal velocity of an aerosol particle undergoing gravitational settling in air.

[0131] "Thiothixene" refers to cis-9-[3-(4-methyl-1-piperazinyl)propylidene]-2-(dimethylsulfonamido)thioxanthene.

[0132] "Thiothixene degradation product" refers to a compound resulting from a chemical modification of thiothixene. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis. An example of a degradation product is a compound of chemical formula C<sub>13</sub>H<sub>9</sub>NO<sub>4</sub>S<sub>2</sub>.

[0133] "Trifluoperazine" refers to 2-trifluoro-methyl-10-[3'-(1-methyl-4-piperazinyl)-propyl]phenothiazine.

[0134] "Trifluoperazine degradation product" refers to a compound resulting from a chemical modification of trifluoperazine. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis. An example of a degradation product is C<sub>11</sub>H<sub>8</sub>NSF<sub>3</sub> (removal of substituted propyl sidechain from nitrogen).

[0135] "Typical patient tidal volume" refers to 1 L for an adult patient and 15 mL/kg for a pediatric patient.

[0136] "Vapor" refers to a gas, and "vapor phase" refers to a gas phase. The term "thermal vapor" refers to a vapor phase, aerosol, or mixture of aerosol-vapor phases, formed preferably by heating.

#### Formation of Antipsychotic Containing Aerosols

[0137] Any suitable method is used to form the aerosols of the present invention. A preferred method, however, involves heating a composition comprising an antipsychotic to form a vapor, followed by cooling of the vapor such that it condenses to provide an antipsychotic comprising aerosol (condensation aerosol). The composition is heated in one of four forms: as pure active compound (*e.g.*, pure olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol or fluphenazine); as a mixture of active compound and a pharmaceutically acceptable excipient; as a salt form of the pure active compound; and, as a mixture of active compound salt form and a pharmaceutically acceptable excipient.

[0138] Salt forms of antipsychotics (*e.g.*, olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine or fluphenazine) are either commercially available or are obtained from the corresponding free base using well known methods in the art. A variety of pharmaceutically acceptable salts are suitable for aerosolization. Such salts include, without limitation, the following: hydrochloric acid, hydrobromic acid, acetic acid, maleic acid, formic acid, and fumaric acid salts.

[0139] Pharmaceutically acceptable excipients may be volatile or nonvolatile. Volatile excipients, when heated, are concurrently volatilized, aerosolized and inhaled with the antipsychotic. Classes of such excipients are known in the art and include, without limitation, gaseous, supercritical fluid, liquid and solid solvents. The following is a list of

exemplary carriers within the classes: water; terpenes, such as menthol; alcohols, such as ethanol, propylene glycol, glycerol and other similar alcohols; dimethylformamide; dimethylacetamide; wax; supercritical carbon dioxide; dry ice; and mixtures thereof.

[0140] Solid supports on which the composition is heated are of a variety of shapes. Examples of such shapes include, without limitation, cylinders of less than 1.0 mm in diameter, boxes of less than 1.0 mm thickness and virtually any shape permeated by small (e.g., less than 1.0 mm-sized) pores. Preferably, solid supports provide a large surface to volume ratio (e.g., greater than 100 per meter) and a large surface to mass ratio (e.g., greater than 1 cm<sup>2</sup> per gram).

[0141] A solid support of one shape can also be transformed into another shape with different properties. For example, a flat sheet of 0.25 mm thickness has a surface to volume ratio of approximately 8,000 per meter. Rolling the sheet into a hollow cylinder of 1 cm diameter produces a support that retains the high surface to mass ratio of the original sheet but has a lower surface to volume ratio (about 400 per meter).

[0142] A number of different materials are used to construct the solid supports. Classes of such materials include, without limitation, metals, inorganic materials, carbonaceous materials and polymers. The following are examples of the material classes: aluminum, silver, gold, stainless steel, copper and tungsten; silica, glass, silicon and alumina; graphite, porous carbons, carbon yarns and carbon felts; polytetrafluoroethylene and polyethylene glycol. Combinations of materials and coated variants of materials are used as well.

[0143] Where aluminum is used as a solid support, aluminum foil is a suitable material. Examples of silica, alumina and silicon based materials include amorphous silica S-5631 (Sigma, St. Louis, MO), BCR171 (an alumina of defined surface area greater than 2 m<sup>2</sup>/g from Aldrich, St. Louis, MO) and a silicon wafer as used in the semiconductor industry. Carbon yarns and felts are available from American Kynol, Inc., New York, NY. Chromatography resins such as octadecyl silane chemically bonded to porous silica are exemplary coated variants of silica.

[0144] The heating of the antipsychotic compositions is performed using any suitable method. Examples of methods by which heat can be generated include the following: passage of current through an electrical resistance element; absorption of electromagnetic radiation, such as microwave or laser light; and, exothermic chemical reactions, such as

exothermic solvation, hydration of pyrophoric materials and oxidation of combustible materials.

#### **Delivery of Antipsychotic Containing Aerosols**

[0145] Antipsychotic containing aerosols of the present invention are delivered to a mammal using an inhalation device. Where the aerosol is a condensation aerosol, the device has at least three elements: an element for heating an antipsychotic containing composition to form a vapor; an element allowing the vapor to cool, thereby providing a condensation aerosol; and, an element permitting the mammal to inhale the aerosol.

Various suitable heating methods are described above. The element that allows cooling is, in its simplest form, an inert passageway linking the heating means to the inhalation means. The element permitting inhalation is an aerosol exit portal that forms a connection between the cooling element and the mammal's respiratory system.

[0146] One device used to deliver the antipsychotic containing aerosol is described in reference to Fig. 1. Delivery device 100 has a proximal end 102 and a distal end 104, a heating module 106, a power source 108, and a mouthpiece 110. An antipsychotic composition is deposited on a surface 112 of heating module 106. Upon activation of a user activated switch 114, power source 108 initiates heating of heating module 106 (e.g., through ignition of combustible fuel or passage of current through a resistive heating element). The antipsychotic composition volatilizes due to the heating of heating module 106 and condenses to form a condensation aerosol prior to reaching the mouthpiece 110 at the proximal end of the device 102. Air flow traveling from the device distal end 104 to the mouthpiece 110 carries the condensation aerosol to the mouthpiece 110, where it is inhaled by the mammal.

[0147] Devices, if desired, contain a variety of components to facilitate the delivery of antipsychotic containing aerosols. For instance, the device may include any component known in the art to control the timing of drug aerosolization relative to inhalation (e.g., breath-actuation), to provide feedback to patients on the rate and/or volume of inhalation, to prevent excessive use (*i.e.*, "lock-out" feature), to prevent use by unauthorized individuals, and/or to record dosing histories.

**Dosage of Antipsychotic Containing Aerosols**

[0148] The dosage amount of antipsychotic in aerosol form is generally no greater than twice the standard dose of the drug given orally. For instance, olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine, or fluphenazine are given at strengths of 10 mg, 7.5 mg to 10 mg, 2 mg, 30 mg to 50 mg, 2 mg to 8 mg, 150 mg, 75 mg, 50 mg to 100 mg, 10 mg, 10 mg to 100 mg, 1 mg, 5 mg, and 1 mg respectively for the treatment of psychosis. As aerosols, 0.2 mg to 20 mg of olanzapine, 0.2 mg to 10 mg trifluoperazine, 0.2 mg to 10 mg of haloperidol, 2 mg to 100 mg of loxapine, 0.1 mg to 5 mg of risperidone, 2 mg to 200 mg of clozapine, 2 mg to 200 mg of quetiapine, 2 mg to 200 mg of promazine, 0.5 mg to 20 mg of thiothixene, 2 mg to 200 mg of chlorpromazine, 0.2 mg to 20 mg of droperidol, 0.5 mg to 20 mg of prochlorperazine, and 0.1 mg to 10 mg of fluphenazine are generally provided per inspiration for the same indication. A typical dosage of an antipsychotic containing aerosol is either administered as a single inhalation or as a series of inhalations taken within an hour or less (dosage equals sum of inhaled amounts). Where the drug is administered as a series of inhalations, a different amount may be delivered in each inhalation.

[0149] One can determine the appropriate dose of antipsychotic containing aerosols to treat a particular condition using methods such as animal experiments and a dose-finding (Phase I/II) clinical trial. One animal experiment involves measuring plasma concentrations of drug in an animal after its exposure to the aerosol. Mammals such as dogs or primates are typically used in such studies, since their respiratory systems are similar to that of a human. Initial dose levels for testing in humans is generally less than or equal to the dose in the mammal model that resulted in plasma drug levels associated with a therapeutic effect in humans. Dose escalation in humans is then performed, until either an optimal therapeutic response is obtained or a dose-limiting toxicity is encountered.

**Analysis of Antipsychotic Containing Aerosols**

[0150] Purity of an antipsychotic containing aerosol is determined using a number of methods, examples of which are described in Sekine *et al.*, *Journal of Forensic Science* 32:1271-1280 (1987) and Martin *et al.*, *Journal of Analytic Toxicology* 13:158-162 (1989). One method involves forming the aerosol in a device through which a gas flow (e.g., air

flow) is maintained, generally at a rate between 0.4 and 60 L/min. The gas flow carries the aerosol into one or more traps. After isolation from the trap, the aerosol is subjected to an analytical technique, such as gas or liquid chromatography, that permits a determination of composition purity.

[0151] A variety of different traps are used for aerosol collection. The following list contains examples of such traps: filters; glass wool; impingers; solvent traps, such as dry ice-cooled ethanol, methanol, acetone and dichloromethane traps at various pH values; syringes that sample the aerosol; empty, low-pressure (*e.g.*, vacuum) containers into which the aerosol is drawn; and, empty containers that fully surround and enclose the aerosol generating device. Where a solid such as glass wool is used, it is typically extracted with a solvent such as ethanol. The solvent extract is subjected to analysis rather than the solid (*i.e.*, glass wool) itself. Where a syringe or container is used, the container is similarly extracted with a solvent.

[0152] The gas or liquid chromatograph discussed above contains a detection system (*i.e.*, detector). Such detection systems are well known in the art and include, for example, flame ionization, photon absorption and mass spectrometry detectors. An advantage of a mass spectrometry detector is that it can be used to determine the structure of antipsychotic degradation products.

[0153] Particle size distribution of an antipsychotic containing aerosol is determined using any suitable method in the art (*e.g.*, cascade impaction). An Andersen Eight Stage Non-viable Cascade Impactor (Andersen Instruments, Smyrna, GA) linked to a furnace tube by a mock throat (USP throat, Andersen Instruments, Smyrna, GA) is one system used for cascade impaction studies.

[0154] Inhalable aerosol mass density is determined, for example, by delivering a drug-containing aerosol into a confined chamber via an inhalation device and measuring the mass collected in the chamber. Typically, the aerosol is drawn into the chamber by having a pressure gradient between the device and the chamber, wherein the chamber is at lower pressure than the device. The volume of the chamber should approximate the tidal volume of an inhaling patient.

[0155] Inhalable aerosol drug mass density is determined, for example, by delivering a drug-containing aerosol into a confined chamber via an inhalation device and measuring

the amount of active drug compound collected in the chamber. Typically, the aerosol is drawn into the chamber by having a pressure gradient between the device and the chamber, wherein the chamber is at lower pressure than the device. The volume of the chamber should approximate the tidal volume of an inhaling patient. The amount of active drug compound collected in the chamber is determined by extracting the chamber, conducting chromatographic analysis of the extract and comparing the results of the chromatographic analysis to those of a standard containing known amounts of drug.

[0156] Inhalable aerosol particle density is determined, for example, by delivering aerosol phase drug into a confined chamber via an inhalation device and measuring the number of particles of given size collected in the chamber. The number of particles of a given size may be directly measured based on the light-scattering properties of the particles. Alternatively, the number of particles of a given size is determined by measuring the mass of particles within the given size range and calculating the number of particles based on the mass as follows: Total number of particles = Sum (from size range 1 to size range N) of number of particles in each size range. Number of particles in a given size range = Mass in the size range/Mass of a typical particle in the size range. Mass of a typical particle in a given size range =  $\pi*D^3*\phi/6$ , where D is a typical particle diameter in the size range (generally, the mean boundary MMADs defining the size range) in microns,  $\phi$  is the particle density (in g/mL) and mass is given in units of picograms ( $g^{-12}$ ).

[0157] Rate of inhalable aerosol particle formation is determined, for example, by delivering aerosol phase drug into a confined chamber via an inhalation device. The delivery is for a set period of time (e.g., 3 s), and the number of particles of a given size collected in the chamber is determined as outlined above. The rate of particle formation is equal to the number of 100 nm to 5 micron particles collected divided by the duration of the collection time.

[0158] Rate of aerosol formation is determined, for example, by delivering aerosol phase drug into a confined chamber via an inhalation device. The delivery is for a set period of time (e.g., 3 s), and the mass of particulate matter collected is determined by weighing the confined chamber before and after the delivery of the particulate matter. The rate of aerosol formation is equal to the increase in mass in the chamber divided by the duration of the collection time. Alternatively, where a change in mass of the delivery

device or component thereof can only occur through release of the aerosol phase particulate matter, the mass of particulate matter may be equated with the mass lost from the device or component during the delivery of the aerosol. In this case, the rate of aerosol formation is equal to the decrease in mass of the device or component during the delivery event divided by the duration of the delivery event.

[0159] Rate of drug aerosol formation is determined, for example, by delivering an antipsychotic containing aerosol into a confined chamber via an inhalation device over a set period of time (e.g., 3 s). Where the aerosol is pure antipsychotic, the amount of drug collected in the chamber is measured as described above. The rate of drug aerosol formation is equal to the amount of antipsychotic collected in the chamber divided by the duration of the collection time. Where the antipsychotic containing aerosol comprises a pharmaceutically acceptable excipient, multiplying the rate of aerosol formation by the percentage of antipsychotic in the aerosol provides the rate of drug aerosol formation.

#### **Utility of Antipsychotic Containing Aerosols**

[0160] The antipsychotic containing aerosols of the present invention are typically used for the treatment of psychosis.

[0161] The following examples are meant to illustrate, rather than limit, the present invention.

[0162] Trifluoperazine, haloperidol, loxapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine dimaleate, and fluphenazine were purchased from Sigma ([www.sigma-aldrich.com](http://www.sigma-aldrich.com)). Risperidone was purchased from Sigma RBI ([www.sigma-aldrich.com](http://www.sigma-aldrich.com)). Quetiapine was purchased as SEROQUEL® tablets from a pharmacy. Clozapine and olanzapine were received as gifts from Reddy/Ceminor. Clozapine and olanzapine are also commercially available (isolation using standard methods in the art from CLOZARIL® and ZYPREXA® respectively). Other antipsychotics can be similarly obtained.

#### **EXAMPLE 1**

##### ***General Procedure for Obtaining Free Base of a Compound Salt***

[0163] Approximately 1 g of salt (e.g., mono hydrochloride) is dissolved in deionized water (~30 mL). Three equivalents of sodium hydroxide (1 N NaOH<sub>aq</sub>) is added dropwise

to the solution, and the pH is checked to ensure it is basic. The aqueous solution is extracted four times with dichloromethane (~50 mL), and the extracts are combined, dried ( $\text{Na}_2\text{SO}_4$ ) and filtered. The filtered organic solution is concentrated using a rotary evaporator to provide the desired free base. If necessary, purification of the free base is performed using standard methods such as chromatography or recrystallization.

## EXAMPLE 2

### *General Procedure for Volatilizing Compounds from Halogen Bulb*

[0164] A solution of drug in approximately 120  $\mu\text{L}$  dichloromethane is coated on a 3.5 cm x 7.5 cm piece of aluminum foil (precleaned with acetone). The dichloromethane is allowed to evaporate. The coated foil is wrapped around a 300 watt halogen tube (Feit Electric Company, Pico Rivera, CA), which is inserted into a glass tube sealed at one end with a rubber stopper. Running 90 V or 108 V (prochlorperazine) of alternating current (driven by line power controlled by a variac) through the bulb for 3.5 s or 2.25 s (prochlorperazine) (drug coating of 0.01 mg to 8 mg) or for 5 s (drug coating >8 mg) affords thermal vapor (including aerosol), which is collected on the glass tube walls. Reverse-phase HPLC analysis with detection by absorption of 225 nm light is used to determine the purity of the aerosol. (When desired, the system is flushed through with argon prior to volatilization.) To obtain higher purity aerosols, one can coat a lesser amount of drug, yielding a thinner film to heat. A linear decrease in film thickness is associated with a linear decrease in impurities.

[0165] Table 1, which follows, provides data from drugs volatilized using the above-recited general procedure.

TABLE 1

Compound	Aerosol Purity	Argon Used
Promazine	97.5%	No
	98.3%	Yes
Olanzapine	100%	No
	99.7%	Yes
Trifluoperazine	98%	No
	98%	Yes
Chlorpromazine	96.5%	No
	97%	Yes

Clozapine	99.1%	No
	99.5%	Yes
Fluphenazine	93%	No
	95%	Yes
Haloperidol	96%	No
	97%	Yes
Loxapine	99.3	No
	99.7	Yes
Quetiapine	99.7%	No
Prochlorperazine	97.5%	No

### EXAMPLE 3

*Particle Size, Particle Density, and Rate of Inhalable Particle Formation  
of Olanzapine Aerosol*

[0166] A solution of 12.9 mg olanzapine in 200  $\mu$ L dichloromethane was spread out in a thin layer on the central portion of a 3.5 cm x 7 cm sheet of aluminum foil. The dichloromethane was allowed to evaporate. The aluminum foil was wrapped around a 300 watt halogen tube, which was inserted into a T-shaped glass tube. Both of the openings of the tube were sealed with parafilm, which was punctured with fifteen needles for flow. The third opening was connected to a 1 liter, 3-neck glass flask. The glass flask was further connected to a large piston capable of drawing 1.1 liters of air through the flask. Alternating current was run through the halogen bulb by application of 90 V using a variac connected to 110 V line power. Within 1 s, an aerosol appeared and was drawn into the 1 L flask by use of the piston, with collection of the aerosol terminated after 6 s. The aerosol was analyzed by connecting the 1 L flask to an eight-stage Andersen non-viable cascade impactor. Results are shown in table 1. MMAD of the collected aerosol was 1.6 microns with a geometric standard deviation of 1.7. Also shown in table 1 is the number of particles collected on the various stages of the cascade impactor, given by the mass collected on the stage divided by the mass of a typical particle trapped on that stage. The mass of a single particle of diameter D is given by the volume of the particle,  $\pi D^3/6$ , multiplied by the density of the drug (taken to be 1 g/cm<sup>3</sup>). The inhalable aerosol particle density is the sum of the numbers of particles collected on impactor stages 3 to 8 divided by the collection volume of 1 L, giving an inhalable aerosol particle density of  $4.5 \times 10^6$

## CLAIMS

1. An aerosol for inhalation therapy, wherein the aerosol comprises particles comprising at least 10 percent by weight of an antipsychotic.
2. An aerosol for inhalation therapy, wherein the aerosol comprises particles comprising at least 10 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine, or fluphenazine.
3. The aerosol according to Claim 2, wherein the aerosol particles have a mass median aerodynamic diameter of less than 3 microns.
4. The aerosol according to Claim 2, wherein the particles comprise less than 2.5 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, clozapine, quetiapine, promazine, chlorpromazine, or fluphenazine degradation products.
5. The aerosol according to Claim 2, wherein the aerosol comprises particles comprising at least 90 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, clozapine, quetiapine, promazine, chlorpromazine, prochlorperazine, or fluphenazine.
6. The aerosol according to Claim 5, wherein the aerosol particles have a mass median aerodynamic diameter less than 2 microns.
7. The aerosol according to Claim 6, wherein the aerosol comprises particles comprising at least 97 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, clozapine, quetiapine, promazine, chlorpromazine, or prochlorperazine.
8. A method of delivering olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol or fluphenazine to a mammal through an inhalation route, wherein the route comprises:

a) heating a composition, wherein the composition comprises at least 5 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol or fluphenazine, to form a vapor; and,

b) allowing the vapor to cool, thereby forming a condensation aerosol comprising particles,  
which is inhaled by the mammal.

9. The method according to Claim 8, wherein the particles comprise at least 10 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol, prochlorperazine, or fluphenazine.

10. The method according to Claim 8, wherein the aerosol particles have a mass median aerodynamic diameter of less than 3 microns.

11. The method according to Claim 8, wherein the particles comprise less than 2.5 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, clozapine, quetiapine, promazine, chlorpromazine, or fluphenazine degradation products.

12. The method according to Claim 10, wherein the aerosol comprises particles comprising at least 90 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, clozapine, quetiapine, promazine, chlorpromazine, prochlorperazine, or fluphenazine.

13. The method according to Claim 12, wherein the aerosol particles have a mass median aerodynamic diameter less than 2 microns.

14. The method according to Claim 13, wherein the aerosol comprises particles comprising at least 97 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, clozapine, quetiapine, promazine, chlorpromazine, prochlorperazine.

15. A kit for delivering olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol or fluphenazine through an inhalation route to a mammal, wherein the kit comprises:

a) a composition comprising at least 5 percent by weight of olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol or fluphenazine; and,

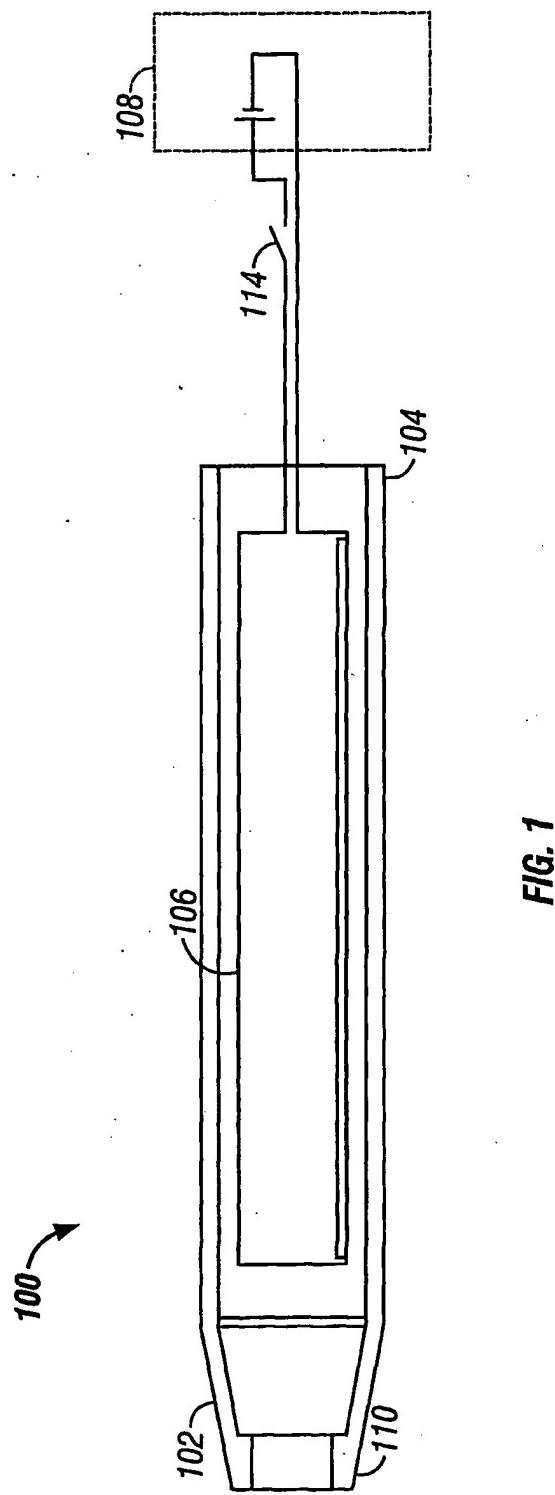
b) a device that forms a olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol or fluphenazine aerosol from the composition, for inhalation by the mammal

and wherein the device comprises:

a) an element for heating the olanzapine, trifluoperazine, haloperidol, loxapine, risperidone, clozapine, quetiapine, promazine, thiothixene, chlorpromazine, droperidol or fluphenazine composition to form a vapor;

b) an element allowing the vapor to cool to form an aerosol; and,

c) an element permitting the mammal to inhale the aerosol.



## INTERNATIONAL SEARCH REPORT

Inte	al Application No
PCT/US 02/16118	

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/72 A61K31/551

According to International Patent Classification (IPC) or to both national classification and IPC
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B. FIELDS SEARCHED
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Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
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EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CHEM ABS Data
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## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 02 24158 A (ADVANCED INHALATION RES INC ;BARTUS RAYMOND T (US); EMERICH DWAINE) 28 March 2002 (2002-03-28) page 7, line 9 - line 23 page 14, line 11 - line 16 page 22, line 1 -page 23, line 16 page 30, line 26 -page 32, line 1	1-7
P, A	---	8-15
X	WO 97 35562 A (WATTS PETER JAMES ;DANBIOSYST UK (GB); ILLUM LISBETH (GB)) 2 October 1997 (1997-10-02) page 13, line 1 - line 28 page 14, line 7 - line 13	1-7
A	---	8-15
	-/-	

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
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- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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9 October 2002	21/10/2002
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Giménez Miralles, J
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## INTERNATIONAL SEARCH REPORT

Inter Application No  
PCT/US 02/16118

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 27359 A (PILKIEWICZ FRANK G) 18 May 2000 (2000-05-18) page 4, line 5 - line 12 page 11, line 17 - line 21 page 14, line 7 -page 15, line 32 page 18, line 16 - line 17 page 19, line 31 -page 20, line 4 -----	1-7
A		8-15

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Continuation of Box I.1

Although claims 8-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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Continuation of Box I.1

Claims Nos.: 8-14

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

# INTERNATIONAL SEARCH REPORT

.....ntional application No.  
PCT/US 02/16118

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 8-14  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2.  Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Inte	al Application No
PCT/US 02/16118	

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
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			HU	0104255 A2		28-03-2002
			PL	347630 A1		22-04-2002
			WO	0027359 A1		18-05-2000

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